REMARKS

Claims 1, 4, 6, 8-11, 13-17, 40-41, and 43-51 are pending in the application. Claims 12 and 18-39 are withdrawn as a result of the restriction requirement. Claims 2, 3, 5, 7 and 42 have been cancelled with this or a previous amendment.

Claims 1 and 4 have been amended to correct ministerial matters. Claims 11 and 46 have been amended, and support for this amendment can be found in the original claims.

Applicants thank the Examiner for the reconsideration and withdrawal of several of the previously pending rejections and objections.

Claims-Objections

Claims 1, 4, 6-11 and 13-17 stand rejected as reciting non-elected subject matter. In response to a requirement for election of species, Applicants elected as a species the cleavage motif IAED (*See* Office Action mailed January 16, 2008). Applicants understand that once this species is found allowable, the remainder of the species will be examined.

Claims 1 and 4 have been amended to correct the ministerial errors noted by the Examiner.

Rejections under 35 USC §112, second paragraph

Claim 11 and 46 rejected as indefinite for allegedly failing to fall within the scope of claims 1 and 40. Applicants have amended claims 11 and 46 to clarify that the Granzyme B used to cleave the fusion protein is one of a human, murine or rat Granzyme B. With this amendment, applicants submit that the rejection is now moot.

Rejections under 35 USC §112, first paragraph, enablement

Claims 7, 8, 42 and 43

Claims 7, 8, 42 and 43 stand rejected under 35 USC 112, first paragraph, for alleged lack of enablement. According to the Examiner, the specification does not reasonably

provide enablement for producing authentic somatotrophin, glucagon, insulin interferon or Granzyme B by cleaving a fusion protein comprising these proteins with Granzyme B.

Applicants have cancelled claims 7 and 42, thereby rendering the rejection moot as to those claims.

With regard to claims 8 and 43, the Examiner is of the opinion that the specification does not provide enablement because the skilled artisan would know that a fusion protein comprising Granzyme B and a Granzyme B cleavage motif would, more likely than not, release Granzyme B by autolysis (the Examiner refers to Example 3).

Applicants disagree with the rejection. Although Example 3 shows autolysis of a fusion protein comprising Granzyme B and a Granzyme B cleavage motif, the Example also shows that autoactivation of this peptide, without the addition of any previously activated Granzyme B, was not completed until after three days at 4 °C. (See specification, paragraph bridging pp. 43-44).

One of skill in the art would readily understand that while autolysis of a fusion protein comprising Granzyme B and a Granzyme B cleavage site may occur, the addition of exogenous Granzyme B to the cleavage reaction would be expected to significantly speed up the reaction. Indeed, the specification teaches the addition of at least a "single molecule" of activated Granzyme B to a mixture of inactivated fusion protein. Accordingly, the Examiner's assertion of lack of enablement is not correct since the skilled artisan would understand that exogenous Granzyme B could be used as a supplement to autolysis. The skilled artisan would also be able to make and use the invention without undue experimentation.

Accordingly, Applicants request that the rejection of claims 8 and 43 be withdrawn.

Rejections under 35 USC §112, first paragraph, written description

Claim 4

Claim 4 stands rejected as lacking written description for the phrase "the penultimate amino acid at the N-terminus of the polypeptide of interest is glycine."

According to the Examiner, this phrase is new matter. Also, in the rejection, the Examiner quotes the specification to the extent that the specification states that the Granzyme B may be used to cleave off polypeptides of interest from fusion proteins without the need for specific amino acids P1'-P4'.

Applicants respectfully disagree with the rejection. The specification need not provide support for the claims *in haec verba*. *See* M.P.E.P. § 21634.02. In the present application, the specification provides ample support for glycine as the penultimate amino acid of the N-terminus of polypeptide of interest. For example, the specification provides an example of a Granzyme B cleavage site -- P4 P3 P2 P1↓P1' P2' -- wherein the P2' is G. (*See* p. 10, first paragraph). Following cleavage at the cleavage site, P2' is the penultimate amino acid of the peptide of interest.

The Examiner's quotation from the specification regarding the lack of need for specific amino acids at P1'-P4' is not relevant to the analysis of written description. Claim 8 depends, ultimately, from claim 1. While the specification supports that none of amino acids P1'-P4' are necessary of Granzyme B cleavage, the use of P1'-P4' is an alternative embodiment that is properly represented in dependent claim 8. The Examiner does not explain how the recited quote supports the rejection for lack of written description.

Accordingly, Applicants respectfully submit that the specification provides sufficient written description support for claim 4. Therefore, Applicants request that the rejection be withdrawn.

Claims 7, 8, 42 and 43

Claims 7, 8, 42 and 43 stand rejected as lacking written description. The examiner asserts that the specification does not describe methods for cleaving fusion proteins having the recited polypeptides. Applicants respectfully disagree and direct the Examiner to the specification, page 11, middle paragraph, as describing each of the polypeptides recited in the claims as a polypeptide of interest.

Applicants have cancelled claims 7 and 42, thereby rendering the rejection moot as to those claims.

With regard to the rejection of claims 8 and 43, the rejection is essentially the same as the rejection of the claims for lack of enablement. Applicants respectfully disagree that the specification lacks written description for an embodiment of the invention wherein a fusion protein including Granzyme B and a Granzyme G cleave site is cleaved with Granzyme B. In particular, the specification describes that, while autoactivation of Granzyme B is contemplated, at least a "single molecule" of active Granzyme G can be added to a cleavage reaction. *See* p. 11, last paragraph. The addition of a "single molecule" of Granzyme B to the cleavage reaction provides support for claims 8 and 43.

Accordingly, Applicants respectfully submit that the specification provides sufficient written description support for claims 8 and 43. Therefore, Applicants request that the rejection be withdrawn.

Rejections under 35 USC §103

Claims 1-4, 9-11, 16-17, 40, 44-46, 50 and 51

Claims 1-4, 9-11, 16-17, 40, 44-46, 50 and 51 stand rejected under 35 U.S.C. 103(a) as obvious over Azad, *et al.* in view of Harris, *et al*, and further in view of Casciola-Rosen, *et al.* According to the Examiner, it would have been obvious to a person of ordinary skill in the art to modify the fusion protein of Azad, *et al.* to incorporate the motif IEAD, as taught by Harris, *et al.* (FIG. 5D) between the GST fusion partner and nef27, and then generate nef27 by cleaving the fusion protein with Granzyme B. The examiner finds the motivation to combine Azad, *et al.* and Harris, *et al.* from the desire to produce nef27. Also, the Examiner also incorrectly states that the Applicants acknowledge that it would have been obvious to cleave a fusion protein with Granzyme B, as was known in the art (referring to Casciola-Rosen, *et al.*).

Applicants respectfully submit that the combination of Azad, *et al.* and Harris, *et al.* does not render obvious the method of independent claims 1 and 40, and the methods of the remainder of the dependent claims. None of the references cited by the Examiner teach the production of a polypeptide in authentic form. In particular, the Examiner acknowledges that Harris, *et al.* does not teach the production of a polypeptide in authentic form. Also, while Casciola-Rosen, *et al.* teaches a number of Granzyme B cleavage motifs,

it does not teach cleavage of fusion proteins or the production of a polypeptide in authentic form.

Moreover, Azad, *et al.* does not describe the production of a polypeptide in authentic form. Attached hereto as Exhibit A is a map of the pGEX-2T fusion vector described in Azad, *et al.* (*See* p. 651, last paragraph). This map shows the thrombin recognition sequence and cleavage site in the GST peptide encoded by the vector: Leu-Val-Pro-Arg↓Gly-Ser, wherein "↓" is the thrombin cleavage site. Therefore, the Nef protein derived from thrombin-cleaved GST-Nef (*see* p. 653) is left with Gly-Ser from the vector at the N-terminus. Because the Nef peptide produced as described in Azad, *et al.* has non-natural Gly-Ser at the N-terminus, Azad, *et al.* does not teach the production of a polypeptide in authentic form as presently claimed.

In order to support a rejection for obviousness, every element of the claims must be found in the prior art or from common knowledge. In this situation, neither the prior art nor the common knowledge teaches the production of a polypeptide in authentic form as presently claimed. Therefore, the cited art does not support the rejection for obviousness, and Applicants request that the rejection be withdrawn.

Claims 1, 4-6, 9-11, 16, 17, 40, 41, 44-46, 50 and 51

Claims 1, 4-6, 9-11, 16, 17, 40, 41, 44-46, 50 and 51 stand rejected under 35 U.S.C. 103(a) as obvious over Azad, *et al.*, Harris, *et al.*, and Casciola-Rosen, *et al.* in view of Boutin, *et al.* According to the Examiner, Boutin, *et al.* teaches a Granzyme B cleavage motif comprising D or E at P4'. Applicants respectfully submit that combination of Azad, *et al.*, Harris, *et al.*, and Casciola-Rosen, *et al.* does not render obvious claim 1 for the reasons addressed above. Boutin, *et al.* does not add to the case of obviousness against independent claims 1 and 40.

The Examiner suggests that Boutin, *et al.* includes a protein beginning with Met-Gly at the N-terminus and that the enzyme calcineurin B has an E at P4'. The Examiner points out that the Met is removed co-translationally. The significance of this event, however, is irrelevant to the rejection or the current claims. The issue is whether one of

skill in the art would prepare a fusion protein having a Granzyme B cleavage motif and enzyme identified in Boutin, *et al.* Applicants submit that the authentic form of calcineurin B does not have a Met at N-terminus because, as the Examiner acknowledges, the Met is removed cotranslationally. Thus, the fusion protein would not have glutamine (E) at P4'. Indeed, none of the peptides in Table 3 of Boutin, *et al.* have E at P4'. Describing nothing more than an enzyme unrelated to Granzyme B, Boutin, *et al.* has nothing to do with enzyme cleave reactions as in the present invention.

Accordingly, Applicants request that the rejection be withdrawn.

Claims 1, 9-11, 13.-17, 40 and 44-51

Claims 1, 9-11, 13.-17, 40 and 44-51 stand rejected under 35 U.S.C. 103(a) as obvious over Azad, *et al.*, Harris, *et al.*, and Casciola-Rosen, *et al.*, in view of Sigma Inc. 1998 or Pharmacia, Inc. Applicants understand that Sigma Inc and Pharmacia Inc are cited as teaching the immobilization of proteases. Sigma Inc. and Pharmacia, Inc. do not, however, cure the deficiency of the combination of Azad, *et al.*, Harris, *et al.*, and Casciola-Rosen, *et al.* to render obvious claims 1 and 40. Therefore, the combination of Sigma, Inc. or Pharmacia, Inc. with Azad, *et al.*, Harris, *et al.*, and Casciola-Rosen *et al.* do not render obvious any of the claims depending from claim 1. Accordingly, Applicants request that the rejection be withdrawn.

CONCLUSION

Applicants submit that all of the rejections and objections in the Office Action have been addressed with the forgoing arguments and amendments. Applicants do not waive any argument by failing to make the argument here. Applicants expressly reserve the right to reassert the above arguments, or assert additional arguments in the future.

Applicants respectfully contend that all conditions of patentability are met in the pending claims as amended. Allowance of the claims is thereby respectfully solicited.

If the Examiner believes it to be helpful, he is invited to contact the undersigned representative by telephone at 312 913 0001.

Respectfully submitted,

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Exhibit A

GE Healthcare

pGEX Vectors, GST Gene Fusion System

Map of the glutathione S-transferase fusion vectors showing the reading frames and main features. Even though stop codons in all three frames are not depicted in this map, all thirteen vectors have stop codons in all three frames downstream from the multiple cloning site.

Do you want to learn more? Read the GST Gene Fusion System Handbook (18-1157-58). Please contact your local GE Healthcare representative for a printed copy.

pGEX-1λT (27-4805-01)

Thrombin

Leu Val Pro Arg↓Gly Ser Pro Glu Phe Ile Val Thr Asp
CTG GTT CCG CGT GGA TCC CCG GAA TTC ATC GTG ACT GAC TGA CGA
BamH I EcoR I Stop codons

pGEX-2T (27-4801-01)

Thrombin

Leu Val Pro Arg↓Gly Ser Pro Gly Ile His Arg Asp
CTG GTT CCG CGT GGA TCC CCG GGA ATT CAT CGT GAC TGA CTG ACG
BamH I Sma I EcoR I Stop codons

pGEX-2TK (27-4587-01)

Thrombin Kinase

Leu Val Pro Arg↓Gly Ser Arg Arg Ala Ser Val
CTG GTT CCG CGT GGA TCT CGT CGT GCA TCT GTT GGA TCC CCG GGA ATT CAT CGT GAC TGA
BamH I Sma I EcoR I Stop codons

pGEX-4T-1 (27-4580-01)

Thrombin

Leu Val Pro Arg↓Gly Ser Pro Glu Phe Pro Gly Arg Leu Glu Arg Pro His Arg Asp
CTG GTT CCG CGT GGA TCC CCG GAA TTC CCG GGT CGA CTC GAG CGG CCG CAT CGT GAC TGA
BamH I EcoR I Sma I Sal I Xho I Not I Stop codons

pGEX-4T-2 (27-4581-01)

Thrombin

Leu Val Pro Arg↓Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser
CTG GTT CCG CGT GGA TCC CCA GGA ATT CCC GGG TCG ACT CGA GCG GCC GCA TCG TGA
BamH I EcoR I Sma I Sal I Xho I Not I Stop codon

pGEX-4T-3 (27-4583-01)

Thrombin

Leu Val Pro Arg↓Gly Ser Pro Asn Ser Arg Val Asp Ser Ser Gly Arg Ile Val Thr Asp
CTG GTT CCG CGT GGA TCC CCG AAT TCC CGG GTC GAC TCG AGC GGC CGC ATC GTG ACT GAC TGA
BamH I EcoR I Sma I Sal I Xho I Not I Stop codons

pGEX-3X (27-4803-01)

Factor Xa

Ile Glu Gly Arg↓Gly Ile Pro Gly Asn Ser Ser
ATC GAA GGT CGT GGG ATC CCC GGG AAT TCA TCG TGA CTG ACT GAC
BamH I Sma I EcoR I Stop codons

pGEX-5X-1 (27-4584-01)

Factor Xa

Ile Glu Gly Arg↓Gly Ile Pro Glu Phe Pro Gly Arg Leu Glu Arg Pro His Arg Asp
ATC GAA GGT CGT GGG ATC CCC GAA TTC CCG GGT CGA CTC GAG CGG CCG CAT CGT GAC TGA
BamH I EcoR I Sma I Sal I Xho I Not I Stop codons

pGEX-5X-2 (27-4585-01)

Factor Xa

Ile Glu Gly Arg↓Gly Ile Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser
ATC GAA GGT CGT GGG ATC CCC GGA ATT CCC GGG TCG ACT CGA GCG GCC GCA TCG TGA
BamH I EcoR I Sma I Sal I Xho I Not I Stop codon

pGEX-5X-3 (27-4586-01)

Factor Xa

Ile Glu Gly Arg↓Gly Ile Pro Arg Asn Ser Arg Val Asp Ser Ser Gly Arg Ile Val Thr Asp
ATC GAA GGT CGT GGG ATC CCC AGG AAT TCC CGG GTC GAC TCG AGC GGC CGC ATC GTG ACT GAC TGA
BamH I EcoR I Sma I Sal I Xho I Not I Stop codons

pGEX-6P-1 (27-4597-01)

PreScission™ Protease

Leu Glu Val Leu Phe Gln↓Gly Pro Leu Gly Ser Pro Glu Phe Pro Gly Arg Leu Glu Arg Pro His
CTG GAA GTT CTG TTC CAG GGG CCC CTG GGA TCC CCG GAA TTC CCG GGT CGA CTC GAG CGG CCG CAT
BamH I EcoR I Sma I Sal I Xho I Not I

pGEX-6P-2 (27-4598-01)

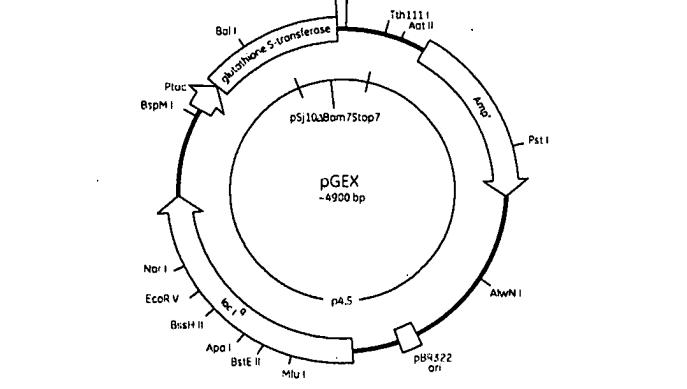
PreScission™ Protease

Leu Glu Val Leu Phe Gln↓Gly Pro Leu Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser
CTG GAA GTT CTG TTC CAG GGG CCC CTG GGA TCC CCA GGA ATT CCC GGG TCG ACT CGA GCG GCC GCA TCG
BamH I EcoR I Sma I Sal I Xho I Not I

pGEX-6P-3 (27-4599-01)

PreScission™ Protease

Leu Glu Val Leu Phe Gln↓Gly Pro Leu Gly Ser Pro Asn Ser Arg Val Asp Ser Ser Gly Arg
CTG GAA GTT CTG TTC CAG GGG CCC CTG GGA TCC CCG AAT TCC CGG GTC GAC TCG AGC GGC CGC
BamH I EcoR I Sma I Sal I Xho I Not I



For contact information for your local office, please visit, www.gelifesciences.com/contact

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First published June 1993.

28-9191-62 AB 05/2007